Intermolecular Benzyne Cycloaddition Approach to Aporphinoids. Total Syntheses of Norcepharadione B, Cepharadione B, Dehydroanonaine, Duguenaine, Dehydronornuciferine, Pontevedrine, *O*-Methylatheroline, Lysicamine, and Alkaloid PO-3

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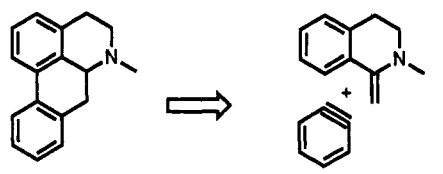
We describe a useful novel approach to the synthesis of aporphinoids, including dehydroaporphines, aristolactams, 4,5-dioxoaporphines, and 7-oxoaporphines, by means of intermolecular benzyne cycloaddition (IBC). Specifically, we report the total synthesis of the isoquinoline alkaloids norcepharadione B, cepharadione B, dehydroanonaine, duguenaine, dehydronornuciferine, pontevedrine, *O*-methylatheroline, lysicamine, and alkaloid PO-3.

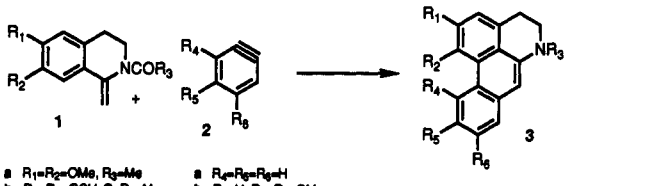
For a number of years, several research groups have devoted considerable effort to developing more efficient syntheses of the various isoquinoline alkaloids. These compounds, which have a wide variety of skeletal arrangements though deriving from quite simple biogenetic precursors, have aroused great interest mainly because of their potential pharmacological properties.[1,2] As part of our continuing work in this field, we embarked some time ago on a program aimed at developing new approaches to the aporphinoids.[3] Most pre-1981 synthetic approaches to these alkaloids may be considered as derived from retrosynthetic analysis involving a hypothetical one-bond disconnection leading to a benzylisoquinoline synthon. In other words, from a synthetic point of view, they share the feature that the strategic biaryl bond is formed in the key final operation. Undoubtedly, the most familiar classical method for achieving this transformation is the well-known Pschorr reaction. Generally, this type of cyclization and other closely related reactions afford aporphinoids in quite low yields (although very recently improvements have been achieved[2,4]). As a result, the past 20 years have witnessed a gradual shift toward the use of photochemistry as the method of choice for carrying out the final cyclization[2,5,6], but since this procedure too does not always give satisfactory results, we decided to investigate a novel, more convergent route derived from a two-bond disconnection (Scheme I), in the hope that it might eventually lead to a general method for most, if not all, classes of aporphinoids. We present here a full account of the results obtained implementing this approach by means of intermolecular benzyne cycloaddition (IBC) between 1-methyleneisoquinolines and arynes, which has allowed us the synthesis of dehydroaporphines,[7,8] 4,5-dioxoaporphines,[7] aristolactams,[7] and oxoaporphines.[9] Optimal conditions have been found for the synthesis of aporphinoids with no ring-D substituents, which can now usually be obtained in 50% yield.[10] The great selectivity of the IBC approach is emphasized, since it allows easy access to the hard to synthesize 11-substituted aporphinoids.[8]

The key IBC step was initially studied by use of the simple models 1, 6, and 8 (Schemes II, III, and IV) in the expectation that they would provide different classes of aporphinoid. The methyleneisoquinolines 1 were prepared in a straightforward manner,[11] *N*-benzyl-3-methylenephthalimidine (8) was prepared as described in the literature,[12] and the isoquinolinedione 6 was synthesized in two steps from the isoquinoline 4[13] by photooxidation in

Scheme I



Scheme II



a R_1=R_2=OMe, R_3=Me
b R_1+R_2=OCH_2O, R_3=Me
c R_1=R_2=OMe, R_3=OEt
d R_1=R_2=OMe, R_3=CF_3
e R_1+R_2=OCH_2O, R_3=CF_3

a R_4=R_5=R_6=H
b R_4=H, R_5=R_6=OMe
c R_4=OMe, R_5=R_6=H

a R_1=R_2=OMe, R_3=COMe, R_4=R_5=R_6=H
b R_1=R_2=OMe, R_3=COOEt, R_4=R_5=R_6=H
c R_1+R_2=OCH_2O, R_3=COMe R_4=R_5=R_6=H
d R_1=R_2=OMe, R_3=$COCF_3$, R_4=R_5=R_6=H
e R_1+R_2=OCH_2O, R_3=$COCF_3$, R_4=R_5=R_6=H
f R_1=R_2=R_4=OMe, R_3=$COCH_3$, R_5=R_6=H
g R_1=R_2=R_4=OMe, R_3=$COCF_3$, R_5=R_6=H
h R_1=R_2=R_5=R_6=OMe, R_3=$COCF_3$, R_4=H
i R_1+R_2=OCH_2O, R_3=R_4=R_5=R_6=H
j R_1=R_2=OMe, R_3=R_4=R_5=R_6=H
k R_1=R_2=R_5=R_6=OMe, R_3=R_4=H
l R_1=R_2=R_4=OMe, R_3=R_5=R_6=H

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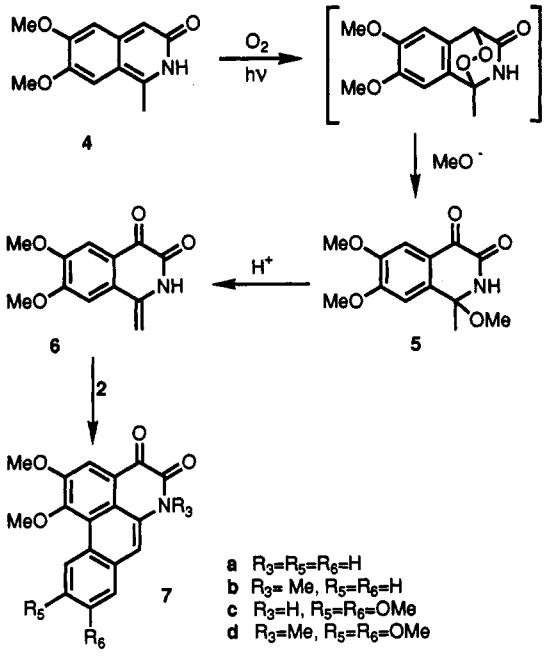
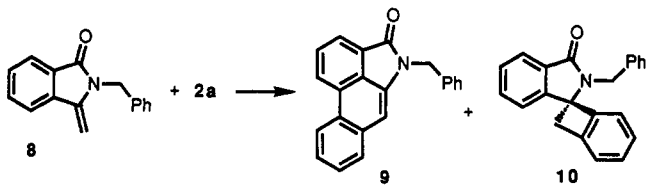
Scheme III



Scheme IV



MeOH, which produced **5** in high yield, followed by acid treatment (Scheme III). Compound **5** was later used as an in situ precursor of the somewhat unstable **6** (see Experimental Section for details).

Our initial attempts to react **1a** with benzyne (**2a**) generated from diphenyliodonium carboxylate[14] or 1-aminobenzotriazol[15] were disappointing. It was eventually found that in situ thermal decomposition of an excess benzenediazonium-2-carboxylate in the presence of **1a** gave the dehydroaporphine **3a** in ca. 40% yield (method A).[16] Similar results were obtained when the 1-methyleneisoquinoline derivatives **1b** and **6** were treated with benzyne by method A, the aporphinoids **3c** and **7a** being obtained in moderate yield. However, when this method was applied to methylenephthalimidine **8** it afforded not only the expected aristolactam **9** (21%) but also the benzocyclobutene derivative **10** (20%). That the [4 + 2] cycloadducts **3**, **7**, and **9** contain a phenanthrene nucleus was confirmed by their characteristic NMR and UV absorption spectra, the former showing a low-field multiplet (H11, aporphine numbering) and a high field singlet (H7).[1,2] A noteworthy feature of all the cyclizations described previously is that no aporphinoids with a dihydrophenanthrene nucleus were ever detected in the reaction mixtures, presumably due to the easy dehydrogenation of the initially formed [4 + 2] cycloadduct.[10f]

The production of the benzocyclobutene **10** raised the question of whether this and related compounds might be

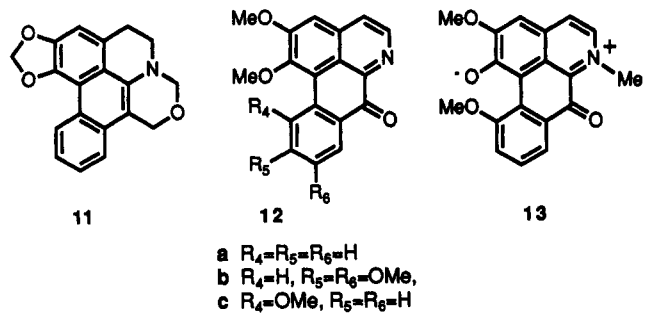


Figure 1.

the precursors of the [4 + 2] cycloadducts. However, attempts to convert the [2 + 2] cycloadduct **10** into the [4 + 2] cycloadduct **9** by heating a solution of **10** in benzene in a sealed tube were completely unsuccessful (^{1}H NMR monitoring), suggesting that benzocyclobutenes are not intermediates in the formation of the [4 + 2] cycloadducts.

Typical byproducts found in all these reactions were biphenylene, acridone, and small amounts of hydrolyzed starting materials. An expedient way of avoiding most of these undesirable reactions was the use of preformed benzenediazonium-2-carboxylate as benzyne precursor (method B).[17] In this manner, the cycloadducts **3a**, **3b**, **7a**, **9**, and **10** were obtained in somewhat improved yields (54, 51, 62, 27, and 63%, respectively).

The dioxoaporphine **7a**, which exhibited the same ^{1}H NMR, MS, UV, and IR characteristics as the natural compound norcepharadione B,[18] was finally converted (NaH, FSO_3Me, DMF) into its *N*-methyl derivative cepharadione B (**7b**).[19] The [4 + 2] cycloadducts **3** can easily be transformed into a variety of aporphinoids (aporphines, noraporphines, oxoaporphines, etc.). For example, reaction of benzyne (method B) with the readily available *N*-(trifluoroacetyl)-1-methylenisoquinoline (**1e**), which is N-protected with a labile group, afforded the dehydroaporphine **3e** (58%); subsequent deprotection with $NaBH_4$ at room temperature provided **3i** in 95% yield and **3i** was converted into the recently isolated duguenaine (**11**)[20] (Figure 1) in 84% yield by treatment with formaldehyde.[21] Remarkably, duguenaine (**11**) was also produced (in 78% yield) when the protected cycloadduct **3e** was reacted directly with formaldehyde for 48 h.

Since many aporphine alkaloids have substituents on ring D, we decided to study IBC with the highly unstable alkoxy-substituted benzynes. Reaction of **6** with 4,5-dimethoxybenzyne (**2b**) by method A gave a 25% yield of the cycloadduct **7c**, which was readily converted into pontevedrine (**7d**)[22] by N-methylation.[22c] Reaction between 6,7-dimethoxy-1-methylene-*N*-(trifluoracetyl)-1,2,3,4-tetrahydroisoquinoline (**1d**) and 4,5-dimethoxybenzene (**2b**) by method A afforded the cycloadduct **3h** in 22% yield.

Encouraged by the previous results, we decided to study the reaction with unsymmetrically substituted benzynes in the hope that it would allow regioselective synthesis of aporphinoids with ring-D substituents. In fulfillment of

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these hopes, reaction of **1a** and **1d** with the unsymmetrically substituted benzyne **2c** (generated in situ[16]) gave the 11-substituted dehydroaporphines **3f** and **3g** regioselectively in 30 and 27% yields, respectively, as deduced from their NMR spectra, which did not show the characteristic low-field H11 signal.[1,2]

To synthesize other aporphinoids, we turned our attention to *N*-(trifluoroacetyl)-1-methyleneisoquinolines. Since only mild reduction conditions are required for removing a trifluoroacetyl group, we expected easy access to the rare dehydronoraporphines and, by subsequent oxidation, to oxoaporphines. As expected, the readily prepared cycloadducts **3d** (61% yield from **1d**) and **3h** (22% yield from **1d**) were easily converted in 75–85% yields into the corresponding dehydronoraporphines **3j** and **3k**, which were finally oxidized by Fremy's salt[23,24] (70–65%) to the oxoaporphines lysicamine[25] (**12a**; 70% yield) and *O*-methylatheroline[25] (**12b**; 65%), respectively. This route to oxoaporphines was also employed to synthesize the quaternary oxoaporphine alkaloid PO-3[26] (Figure 1), the only one of a series of highly colored compounds having a methoxy group at C11. The first total synthesis of alkaloid PO-3 was achieved regioselectively in 8% overall yield (not optimized) by the sequence of reactions **1d** + **2c** → **3g** → **3l** (Scheme II) followed by the use of well-established methods[22a,27] to carry out the sequence of **3l** → **12c** → PO-3 (**13**) (Figure 1).

Experimental Section

General Procedures. All melting points were determined in a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on either Bruker WM-250 (250-MHz) or Varian CFT-20 (80-MHz) spectrometers with $CDCl_3$ (unless otherwise noted) as solvent and $SiMe_4$ as internal standard. Ultraviolet–visible spectra were run on a Pye-Unicam 1700 instrument. Infrared spectra were recorded in KBr pellets with a Pye-Unicam 1100 spectrometer. Low- and high-resolution mass spectra were recorded on Kratos MS-25 and Kratos MS 50 spectrometers, respectively, both operating at 70 eV. Combustion analyses were performed in Perkin-Elmer 240B at the Inorganic Chemistry Department and at the Servei de Microanalisi of the CSIC (Barcelona). Solvents were dried by use of standard procedures.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-methylene-2-(trifluoroacetyl)isoquinoline (1d). Trifluoroacetic anhydride (2.17 g, 10.35 mmol) in pyridine (5 mL) was added to an ice-cooled stirred solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[11] (1.77 g, 8.63 mmol) in dry pyridine (5 mL). Stirring was continued for 30 min at room temperature. Dichloromethane was added and the organic layer washed with 10% $CuSO_4$ solution. The organic phase was dried and finally evaporated to dryness to give **1d** (1.82 g, 70% yield), which crystallized from diethyl ether: mp 68–70 °C; UV (MeOH) λ_{max} 220, 264, 306 nm; IR (KBr) 1700 cm^{-1}; ^1H NMR (80 MHz) 2.93 (t, J = 5.9 Hz, 2 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 3.90–4.10 (m, 2 H), 5.27 (s, 1 H), 5.63 (s, 1 H), 6.58 (s, 1 H), 7.02 (s, 1 H) ppm; MS *m/e* 301 (M^+, 72), 232 (71), 204 (90), 69 (90). HRMS calcd for $C_{14}H_{14}F_3NO_3$ 301.09257, found 301.09370.

[1,3]Benzodioxolo[4,5-*g*]-1,2,3,4-tetrahydro-1-methylene-2-(trifluoroacetyl)isoquinoline (1-Methylene-6,7-(methylenedioxy)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline, 1e). Trifluoroacetic anhydride (2.26 g, 10 mmol) in pyridine (3 mL) was added to an ice-cooled stirred solution of 1-methyl-6,7-(methylenedioxy-3,4-dihydroisoquinoline[28] (1.7 g, 9.0 mmol) in dry pyridine (5 mL). Stirring was continued for 1 h at room temperature. Dichloromethane was added and the organic layer washed with 10% $CuSO_4$ solution. The organic phase was dried and finally evaporated to dryness to give **1e** (2.1 g, 82% yield), which crystallized from diethyl ether: mp 124–126 °C; UV (MeOH) λ_{max} 220, 260, 306 nm; IR (KBr) 1690 cm^{-1}; ^1H NMR (80 MHz) 2.90 (t, J = 6.1 Hz, 2 H), 4.00 (m, 2 H), 5.21 (s, 1 H), 5.57 (s, 1 H), 5.96 (s, 2 H), 6.57 (s, 1 H), 7.01 (s, 1 H) ppm; MS *m/e* 285 (M^+, 100), 216 (85), 188 (94), 69 (43). HRMS calcd for $C_{13}H_{10}F_3NO_3$ 285.06127, found 285.06240.

1,2,3,4-Tetrahydro-1,6,7-trimethoxy-1-methylisoquinoline-3,4-dione (5). A solution of 6,7-dimethoxy-1-methylisoquinolin-3-one[13] (1 g, 4.8 mmol) and NaOMe (1 g, 25 mmol) in dry MeOH (1 L) was saturated with O_2 and irradiated with a medium-pressure mercury lamp for several hours. The reaction mixture was neutralized with ammonium chloride solution, concentrated to 50 mL, and poured into water (200 mL). The resulting solution was extracted with dichloromethane, and the organic extracts were washed with water, dried, and evaporated in vacuo. The residue was crystallized from MeOH, yielding 1,6,7-trimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3,4-dione (**5**; 1.08 g, 85%): mp 150 °C dec; UV (MeOH) λ_{max} 222, 247, 305, 341 nm; IR (KBr) 1700, 1690 cm^{-1}; ^1H NMR (80 MHz) 1.86 (s, 3 H), 3.02 (s, 3 H), 3.96 (s, 3 H), 4.00 (s, 3 H), 6.90 (s, 1 H), 7.54 (s, 1 H) ppm; HRMS calcd for $C_{13}H_{15}NO_5$ 265.09501, found 265.09420. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.85; H, 5.70; N, 5.28. Found: C, 59.44; H, 5.89; N, 5.93.

Reaction of the 1-Methyleneisoquinolines 1 and 6 and the Isoindole Derivative 8 with Benzyne Generated in Situ (Method A). General Procedure.[16] A three-necked flask provided with a reflux condenser and two addition funnels (with drying tubes) was loaded with a 1 mmol solution of **1**, **5** (an excellent precursor of the required 6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline-3,4-dione, **6**), or **8** in dry DME (or dioxane in the case of **8**) and a catalytic amount of trichloroacetic acid and heated to reflux. At this point, dropwise addition of solutions of anthranillic acid and isoamyl nitrite in DME from the addition funnels was started. Addition was stopped when starting material was no longer detected (TLC) in the reaction mixture (~90 min). The resulting solution was cooled and evaporated to dryness. The residue was dissolved in dichloromethane, washed with 5% HCl solution, 5% NaOH, and water, and finally dried over anhydrous sodium sulfate. Evaporation to dryness usually provided a crude residue that was chromatographed on silica gel plates with dichloromethane as eluent.

6-Acetyl-5,6-dihydro-1,2-dimethoxy-4*H*-dibenzo[*de*,*g*]-quinoline (*N*-Acetyl-6a,7-dehydronornuciferine, 3a). Application of the general procedure to compounds **1a**[11] (330 mg, 1.33 mmol) and **2a** (prepared from anthranillic acid (411 mg, 3 mmol) and isoamyl nitrite (413 mg, 3.5 mmol)) gave **3a** as white crystals: mp 94–96 °C (hexane–ether) in 40% yield; UV (EtOH) λ_{max} 260, 312 (sh), 322, 351, 369 nm; IR (KBr) 1625 cm^{-1}; ^1H NMR (80 MHz) 2.30 (s, 3 H), 3.19 (m, 2 H), 3.93 (s, 3 H), 4.02 (s, 3 H), 4.19 (m, 2 H), 7.13 (s, 1 H), 7.29–7.76 (m, 4 H), 9.54–9.56 (m, 1 H) ppm; MS *m/e* 321 (M^+, 35), 306 (3), 279 (15), 43 (100). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.35; H, 5.77; N, 4.24.

6-Acetyl-5,6-dihydro-4*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline (*N*-Acetyl-6a,7-dehydroanonaine, 3c). Application of the general procedure to **1b**[28] (1 g, 4.3 mmol) and **2a** (generated from anthranillic acid (3.56 g, 26 mmol) and isoamyl nitrite (4.59 g, 39 mmol)) yielded **3c** as a crystalline solid of mp 155–157 °C (ethyl acetate–hexane) in 36% isolated yield: UV (EtOH) λ_{max} 252, 290, 320, 356, 376 nm; IR (KBr) 1650 cm^{-1}; ^1H NMR (80 MHz) 2.29 (s, 3 H), 3.10 (t, J = 5.7 Hz, 2 H), 4.13 (t, J = 5.7 Hz, 2 H), 6.20 (s, 2 H), 6.98 (s, 1 H), 7.25–7.76 (m, 4 H), 9.00–9.04 (m, 1 H); MS *m/e* 305 (M^+), 43 (100). HRMS calcd for $C_{19}H_{15}NO_3$ 305.10519, found 305.10500.

6-Acetyl-5,6-dihydro-1,2,11-trimethoxy-4*H*-dibenzo[*de*,*g*]quinoline (*N*-Acetyl-1,2,11-trimethoxy-6a,7-dehydronoraporphine, *N*-Acetylnororientidine, 3f). Reaction of **1a** with

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2c was carried out as illustrated in the general procedure from 1a[11] (0.5 g, 2 mmol), 2-amino-6-methoxybenzoic acid[30] (1.35 g, 8 mmol) and isoamyl nitrite (1.04 g, 8.8 mmol). Standard workup provided **3f** in 28% yield: mp 122–4 °C (absolute ethanol); UV (EtOH) λ_{max} 218, 266, 296, 334, 360, 380 nm; IR (KBr) 1650 cm^{-1}; ^1H NMR (80 MHz) 2.28 (s, 3 H), 3.16 (t, J = 5.9 Hz, 2 H), 3.60 (s, 3 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 4.19 (t, J = 5.9 Hz, 2 H), 6.99–7.51 (m, 5 H); MS m/e 351 (M^+, 100), 308 (33), 43 (100); HRMS calcd for $C_{21}H_{21}NO_4$ 351.14760, found 351.1476. Anal. Calcd for $C_{21}H_{21}NO_4 \cdot 1/2\ H_2O$: C, 69.99; H, 6.15; N, 3.89. Found: C, 71.00; H, 6.19; N, 3.94.

5,6-Dihydro-1,2,11-trimethoxy-6-(trifluoroacetyl)-4*H*-dibenzo[*de*,*g*]quinoline (*N*-(Trifluoroacetyl)-1,2,11-trimethoxy-6a,7-dehydronoraporphine, *N*-(Trifluoroacetyl)-dehydronororientidine, 3g). Reaction of **1d** (0.2 g, 0.664 mmol) with **2c** (generated from 2-amino-6-methoxybenzoic acid[30] (0.665 g, 3.98 mmol) and isoamyl nitrite (0.56 g, 4.78 mmol)) furnished, after chromatography, 27% yield of **3g** as colorless crystals of mp 170–1 °C (absolute ethanol): UV (MeOH) λ_{max} 262, 298, 334, 362, 390 nm; IR (KBr) 1690 cm^{-1}; ^1H NMR (250 MHz) 3.29 (t, J = 5.8 Hz, 2 H), 3.60 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.15 (m, 2 H), 7.04 (dd, J = 7.8 and 1.1 Hz, 1 H), 7.05 (s, 1 H), 7.15–7.22 (m, 1 H), 7.35 (dd, J = 7.8 and 1.1 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H) ppm; MS m/e 405 (M^+, 100), 362 (16), 69 (20); HRMS calcd for $C_{21}H_{18}F_3NO_4$ 405.11878, found: 405.1198. Anal. Calcd for $C_{21}H_{18}F_3NO_4 \cdot 1/4H_2O$: C, 61.54; H, 4.55; N, 3.42. Found: C, 61.61; H, 4.35; N, 4.12.

5,6-Dihydro-1,2,9,10-tetramethoxy-6-(trifluoroacetyl)-4*H*-dibenzo[*de*,*g*]quinoline (*N*-(Trifluoroacetyl)-1,2,9,10-tetramethoxy-6a,7-dehydronoraporphine, *N*-(Trifluoroacetyl)dehydronorglaucine, 3h). Reaction of **1d** (0.25 g, 0.83 mmol) with **2b** (generated from 2-amino-4,5-dimethoxybenzoic acid (1.5 g, 7.6 mmol) and isoamyl nitrite (1.12 g, 9.57 mmol)) furnished a crude mixture that on chromatography yielded **3h** (22%): mp 176–8 °C (absolute ethanol); UV (MeOH) λ_{max} 256, 284 (sh), 320, 350, 366 nm; IR (KBr) 1680 cm^{-1}; ^1H NMR (250 MHz) 3.31 (m, 2 H), 3.93 (s, 3 H), 4.03 (s, 3 H), 4.04 (s, 3 H), 4.07 (s, 3 H), 4.15 (m, 2 H), 7.10 (s, 1 H), 7.19 (s, 1 H), 7.90 (s, 1 H), 9.21 (s, 1 H) ppm. Anal. Calcd for $C_{22}H_{20}NO_5F_3$: C, 60.68; H, 4.59; N, 3.21. Found: C, 60.51; H, 4.74; N, 2.75.

5,6-Dihydro-1,2-dimethoxy-4*H*-dibenzo[*de*,*g*]quinoline-4,5-dione, (Norcepharadione B, 7a). This compound was obtained in 40% yield by the general procedure by reacting compound **5** (375 mg, 1.5 mmol), trichloroacetic acid (40 mg, 0.25 mmol), and **2a** (generated from anthranillic acid (600 mg, 4.38 mmol) and isoamyl nitrite (825 mg, 7.42 mmol)); yellow crystals (DMF, 90 °C); mp 304–307 °C dec (lit.[18] mp 305–307 °C dec).

5,6-Dihydro-1,2-dimethoxy-6-methyl-4*H*-dibenzo[*de*,*g*]-quinoline-4,5-dione (Cepharadione B, 7b). Under an inert atmosphere, hexane-washed NaH (50 mg, 2 mmol) was added to a solution of norcepharadione B (**7a**; 36 mg, 0.1 mmol) in dry DME. Methyl fluorosulfonate (0.25 mL, 2 mmol) was added to the resulting mixture with a syringe. After the solution was stirred for 2 h, MeOH was added and the resulting solution was acidified with 5% HCl and extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel plates to give **7b** (24 mg, 65% yield), whose spectroscopic data were in complete agreement with those of an authentic sample, mp 266–268 °C (lit.[19] mp 267–268 °C).

5,6-Dihydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de*,*g*]-quinoline-4,5-dione (Pontevedrine, 7d). Reaction of isoquinolinedione **5** with 4,5-dimethoxybenzyne (**2b**) led to isoquinolinedione **7c** (20% yield), which crystallized from EtOH–EtOEt, mp 284–286 °C (lit.[22c] mp 284–286 °C).

Pontevedrine **7d** was obtained from compound **7c** following the reported procedure,[22c] mp 269–271 °C (lit.[22a] mp 269–271 °C).

1-Benzyldibenzo[*cd*,*f*]-2*H*-indol-2-one (Aristolactam, 9). Reaction of the phthalimidine **8**[12] with benzyne as illustrated in the general procedure furnished a mixture of **9** and **10**, which were isolated by chromatography. The aristolactam **9** was obtained in 27% yield as yellow crystals of mp 174–6 °C (EtOH): UV (EtOH) λ_{max} 224, 233 (sh), 246, 286, 298, 316 (sh) nm; IR (KBr) 1720, 1650 cm^{-1}; ^1H NMR (80 MHz) 5.19 (s, 2 H), 6.97 (s, 1 H), 7.27–8.11 (m, 10 H), 8.40–8.65 (m, 2 H) ppm; MS m/e 309 (M^+, 8), 218 (5), 191 (17), 91 (100). Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 84.79; H, 4.95; N, 4.27.

The benzocyclobutene **10** was obtained in 20% yield as an oil: UV (EtOH) λ_{max} 250 (sh), 266 (sh), 272, 282 (sh) nm; IR (KBr) 1690 cm^{-1}; ^1H NMR (80 MHz) 3.50 (s, 2 H), 4.46 (d, J = 15.3 Hz, 1 H), 4.82 (d, J = 15.3 Hz, 1 H), 6.57 (d, J = 7.0 Hz, 1 H), 7.14–7.54 (m, 11 H), 7.91–7.97 (m, 1 H) ppm; ^{13}C NMR 42.78 (t), 43.36 (t), 70.89 (s), 120.89 (d), 122.46 (d), 123.02 (d), 123.30 (d), 126.97 (d), 127.67 (d), 128.14 (d), 129.91 (d), 130.94 (s), 131.83 (d), 138.28 (s), 141.68 (s), 144.33 (s), 147.37 (s), 168.06 (s) ppm; MS m/e 311 (M^+, 26), 296 (46), 282 (44), 160 (40), 91 (100). Anal. Calcd for $C_{22}H_{17}NO \cdot 1/2H_2O$: C, 82.50; H, 5.62; N, 4.37. Found: C, 82.68; H, 6.04; N, 4.17.

Reaction of the 1-Methyleneisoquinolines 1 and 6 and the Isoindole 8 with Benzyne Generated by Heating the Preformed Benzenediazonium-2-carboxylate Salt (Method B). General Procedure.[17] Excess isoamyl nitrite was added over 1–2 min to an ice-cooled stirred solution of anthranillic acid (5–10 equiv) in dry DME containing a catalytic amount of trichloroacetic acid. The ice bath was removed after 15 min, and the mixture turned brown-red as it reached room temperature. This mixture was stirred for 90 min. After dilution with DME, the supernatant layer was discarded (*aspiration through Teflon tubing into a plastic syringe is recommended*). **Caution: when dry, benzenediazonium-2-carboxylate detonates violently on being scraped or heated.** The remaining material was washed several times with DME until neutral. The resulting brownish precipitate was suspended in solvent and with the aid of a *plastic syringe with Teflon tubing* (*never with a metal needle*!) was added slowly to a refluxing solution of the 1-methyleneisoquinoline or isoindole derivatives in DME. The reaction was monitored by TLC until the starting material disappeared. The solvent was then removed "in vacuo" and the residue chromatographed on silica gel plates (typically with dichloromethane as eluent).

6-Acetyl-5,6-dihydro-1,2-dimethoxy-4*H*-dibenzo[*de*,*g*]-quinoline (*N*-Acetyl-6a,7-dehydronornuciferine, 3a). This compound was obtained in 53% yield by reacting **1a**[11] (200 mg, 0.81 mmol) and **2a** prepared from anthranillic acid (353 mg, 2.6 mmol) and isoamyl nitrite (495 mg, 4.23 mmol).

6-(Ethoxycarbonyl)-5,6-dihydro-1,2-dimethoxy-4*H*-dibenzo[*de*,*g*]quinoline (*N*-Carbethoxy-6a,7-dehydronornuciferine, 3b). This compound was obtained as colorless crystals by reacting *N*-carbethoxy-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline[6] (**1c**; 250 mg, 0.9 mmol) with **2a** generated from anthranillic acid (727 mg, 5.31 mmol) and isoamyl nitrite (993 mg, 8.5 mmol), mp 112–4 °C (lit.[29] mp 128–130 °C).

5,6-Dihydro-1,2-dimethoxy-6-(trifluoroacetyl)-4*H*-dibenzo[*de*,*g*]quinoline (*N*-(Trifluoroacetyl)-6a,7-dehydronornuciferine, 3d). Reaction of **1d** (0.4 g, 1.33 mmol) and benzyne (**2a**) generated by thermal decomposition of preformed benzenediazonium-2-carboxylate prepared from anthranillic acid (2.14 g, 15 mmol) and isoamyl nitrite (2.19 g, 18 mmol) furnished **3d** in 62% yield: mp 134–6 °C (EtOH); UV (MeOH) λ_{max} 256, 284 (sh), 320, 350, 368 nm; IR (KBr) 1690 cm^{-1}; ^1H NMR (80 MHz) 3.31 (t, J = 5.5 Hz, 2 H), 3.93 (s, 3 H), 4.02 (s, 3 H), 4.18 (t, J = 5.5 Hz, 2 H), 7.13–7.16 (m, 2 H), 7.54–7.88 (m, 3 H), 9.53–9.65 (m, 1 H) ppm; MS m/e 375 (M^+, 100), 360 (50), 220 (71), 69 (80). Anal. Calcd for $C_{20}H_{16}NO_3F_3$: C, 64.0; H, 3.73; N, 4.26. Found: C, 64.1; H, 3.68; N, 4.35.

6-(Trifluoroacetyl)-5,6-dihydro-4*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline (*N*-(Trifluoroacetyl)-6a,7-dehydroanonaine, 3e). Reaction of **1e** (0.6 g, 2.1 mmol) with benzyne (**2a**) generated from anthranillic acid (2.18 g, 16 mmol) and isoamyl nitrite (2.36 g, 20 mmol) yielded 440 mg of *N*-(trifluoroacetyl)-dehydroanonaine (**3e**; 58%): mp 158–160 °C (MeOH); UV (EtOH), λ_{max} 252, 312, 320, 354, 370 nm; IR (KBr) 1650 cm^{-1}; ^1H NMR (250 MHz) 3.25 (t, J = 5.6 Hz, 2 H), 4.13 (m, 2 H), 6.25 (s, 2 H), 7.03 (s, 1 H), 7.61–7.57 (m, 3 H), 7.82–7.79 (m, 1 H), 9.02–8.99 (m, 1 H) ppm; MS m/e 359 (M^+, 100), 344 (50), 204 (68), 69 (75). Anal. Calcd for $C_{19}H_{12}NF_3O_3$: C, 63.50; H, 3.34; N, 3.89. Found: C, 63.28; H, 3.66; N, 3.78.

5,6-Dihydro-1,2-dimethoxy-4*H*-dibenzo[*de*,*g*]quinoline-4,5-dione (Norcepharadione B, 7a). This was prepared in 62% yield by method B by heating a solution of 1-methyl-1,6,7-tri-

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methoxyisoquinoline-3,4-dione (5; 200 mg, 0.75 mmol) in DME (10 mL) containing trichloroacetic acid (20 mg, 0.125 mmol) with 2a generated from anthranillic acid (608 mg, 4.43 mmol) and isoamyl nitrite (855 mg, 7.31 mmol).

1-Benzyldibenzo[*cd*,*f*]-2*H*-indol-2-one (Aristolactam, 9). Reaction of *N*-benzyl-3-methylenephthalimidine[12] (8; 235 mg, 1 mmol) and benzyne (2a, generated from anthranillic acid (800 mg, 5.8 mmol) and isoamyl nitrite (1.12 g, 9.57 mmol) furnished compounds 9 (84 mg, 27% isolated yield) and 10 (194 mg, 63% isolated yield).

9,10-Dihydro-5*H*,7*H*-benzo[*f*][1,3]dioxolo[6,7]isoquino-[8,1,2-*hij*][3,1]benzoxazine (Duguenaine, 11). A stirred solution of (trifluoroacetyl)dehydroanonaine (3e; 100 mg, 0.27 mmol) in dry EtOH (15 mL) was reacted with $NaBH_4$ (excess). When the reaction was over (TLC, 10 min), the mixture was concentrated to dryness and the residue dissolved in dichloromethane (25 mL) and washed with water (3 × 10 mL). Evaporation of the dichloromethane gave 6a,7-dehydroanonaine (3i)[21] as an oil (70 mg, 95%) that was converted into duguenaine[20] (11; 68 mg, 84%) following the reported procedure.[21]

1,2-Dimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (Lysicamine, 12a). $NaBH_4$ (excess) was added portionwise to a solution of 3d (50 mg, 0.13 mmol) in absolute EtOH (10 mL). After 5 min, the reaction was over (TLC monitoring). The usual workup gave dehydronornuciferine (3j,[21] 37 mg, quantitative).

To a solution of crude dehydronornuciferine (3j; 20 mg, 0.072 mmol) in methanol (10 mL) was added excess Fremy's salt[24] in 4% aqueous sodium carbonate. After the solution was stirred overnight, the usual workup[23] yielded 12a (15 mg, 70%), which was identical in all respects with an authentic sample of lysicamine.[25]

1,2,9,10-Tetramethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (*O*-Methylatheroline, 12b). Successive lots of sodium borohydride were added to a solution of 3h (35 mg, 0.08 mmol) in absolute ethanol (10 mL). The reaction was over (TLC) in ca. 5 min. Standard extractive workup provided dehydronorglaucine (3k,[21] 18 mg, 67% yield).

A solution of crude dehydronorglaucine (3k; 13 mg, 0.04 mmol) in 10 mL of MeOH was treated with excess Fremy's salt[24] in 4% aqueous sodium carbonate and stirred overnight. The usual Workup[23] yielded 12b (6 mg, 30%), identical in all respects with an authentic sample of *O*-methylatheroline.[25]

1-Oxy-2,11-dimethoxy-6-methyl-7-oxo-7*H*-dibenzo[*de*,*g*]-quinolinium (Alkaloid PO-3, 13). Sodium borohydride (excess) was added portionwise to a solution of 3g (29 mg, 0.072 mmol) in ethanol (10 mL). After 5 min, the reaction was over (TLC monitoring). The usual workup furnished a quantitative yield of 1,2,11-trimethoxydehydronoraporphine (nororientidine, 3l), which was used in the next step without further purification: ^{1}H NMR (250 MHz) 3.20 (t, J = 5.9 Hz, 2 H), 3.46 (t, J = 5.9 Hz, 2 H), 3.56 (s, 3 H), 4.00 (s, 6 H), 6.47 (s, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 7.01 (s, 1 H), 7.12 (d, J = 7.8 Hz, 1 H), 7.38 (t, J = 7.8 Hz, 1 H) ppm.

To a stirred solution of 3l (19 mg, 0.06 mmol) in methanol was added excess Fremy's salt[24] dissolved in 4% aqueous sodium carbonate, and the mixture was stirred for 18 h. After the usual workup,[23] oxoaporphine 12c was isolated (14 mg, 71%): ^{1}H NMR (250 MHz) 3.73 (s, 3 H), 4.00 (s, 3 H), 4.08 (s, 3 H), 7.13 (s, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.55 (t, J = 7.9 Hz, 1 H), 7.74 (d, J = 5.2 H, 1 Hz), 8.10 (d, J = 7.9 Hz, 1 H), 8.81 (d, J = 5.2 Hz, 1 H) ppm; MS m/e 321 (M^+, 100). HRMS calcd for $C_{19}H_{14}NO_4$ 321.10010, found, 321.09990.

The crude oxoaporphine 12c (14 mg) was dissolved in acetone (10 mL), treated with excess methyl iodide, and stirred for 24 h at room temperature. The resulting methiodide (16 mg, 79%) was used without purification in the next step: ^{1}H NMR (250 MHz) 3.88 (s, 3 H), 4.02 (s, 3 H), 4.27 (s, 3 H), 4.82 (s, 3 H), 7.39 (d, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.88–7.91 (s+d, J = 8 Hz, 2 H), 8.90 (d, J = 5.8 Hz, 1 H), 9.22 (d, J = 5.8 Hz, 1 H) ppm.

The previous methiodide was heated in refluxing acetone for 24 h. The resulting green solution was evaporated to dryness. The residue obtained was chromatographed on silica gel plates (CH_2Cl_2:MeOH = 9:1), giving alkaloid PO-3 (13; 7 mg) and 1 mg of 1,2,11-trimethoxyoxoaporphine (12c). The synthetic PO-3 exhibited properties identical with those reported[26] (an authentic sample was not available).

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Registry No. 1a, 57621-04-2; 1b, 92029-23-7; 1c, 82044-05-1; 1d, 101064-78-2; 1e, 132646-13-0; 2a, 462-80-6; 2b, 54632-05-2; 2c, 33543-19-0; 3a, 82359-82-8; 3b, 13555-30-1; 3c, 132646-11-8; 3d, 101064-64-6; 3e, 132646-12-9; 3f, 86826-87-1; 3g, 101064-65-7; 3h, 101064-63-5; 3i, 41679-82-7; 3j, 92664-95-4; 3k, 39945-38-5; 3l, 101124-45-2; 4, 16535-98-1; 5, 82359-80-6; 7a, 57576-41-7; 7b, 55610-02-1; 7c, 68244-16-6; 7d, 34647-65-9; 8, 82359-81-7; 9, 82359-83-9; 10, 132646-14-1; 11, 80550-24-9; 12a, 15444-20-9; 12b, 5574-24-3; 12c, 101064-62-4; 13, 101064-66-8; 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 4721-98-6; 1-methyl-6,7-(methylenedioxy)-3,4-dihydroisoquinoline, 17104-27-7; anthranilic acid, 118-92-3; 2-amino-6-methoxybenzoic acid, 53600-33-2; 2-amino-4,5-dimethoxybenzoic acid, 5653-40-7; benzenediazonium-2-carboxylate, 1608-42-0.

Supplementary Material Available: NMR spectra of compounds 1d, 1e, 3c, 3l, and 11c (6 pages). Ordering information is given on any current masthead page.

Syntheses of (±)-α- and (±)-γ-Lycorane via a Stereocontrolled Organopalladium Route

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Total syntheses of (±)-α- and (±)-γ-lycorane are described. The key steps in the syntheses are the stereocontrolled palladium-catalyzed intramolecular 1,4-chloroamidation of 12 to 13 and the subsequent anti-stereoselective copper-catalyzed S_N2' reaction of allylic chloride 13 with [3,4-(methylenedioxy)phenyl]magnesium bromide to give 14. Hexahydroindole 14 has the required relative stereochemistry between carbons 3a, 7, and 7a for α-lycorane (1a) and was transformed to the latter via 15 and 16. The epimeric γ-lycorane (2) was obtained by performing the Bischler–Napieralski cyclization on 14, which led to a highly stereoselective isomerization to give exclusively 17. Compound 17 was subsequently transformed to 2. The overall yield from ester 8 to (±)-α- and (±)-γ-lycorane was 40 and 36%, respectively.

The amaryllidaceae alkaloids constitute an important class of naturally occurring compounds.[1] In particular, the lycorine-type alkaloids have attracted considerable interest and a number of total syntheses of the latter have

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